RESEARCH ETHICS

Should desperate volunteers be included in randomised controlled trials?

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Randomised controlled trials (RCTs) sometimes recruit participants who are desperate to receive the experimental treatment. This paper defends the practice against three arguements that suggest it is unethical first, desperate volunteers are not in equipoise. Second clinicians, entering patients onto trials are disavowing their therapeutic obligation to deliver the best treatment; they are following trial protocols rather than delivering individualised care. Research is not treatment; its ethical justification is different. Consent is crucial. Third, desperate volunteers do not give proper consent: effectively, they are coerced. This paper responds by advocating a notion of equipoise based on expert knowledge and widely shared values. Where such collective, expert equipoise exists there is a prima facie case for an RCT. Next the paper argues that trial entry does not involve clinicians disavowing their therapeutic obligation; individualised care based on insufficient evidence is not in patients best interest. Finally, it argues that where equipoise exists it is acceptable to limit access to experimental agents; desperate volunteers are not coerced because their desperation does not translate into a right to receive what they desire.

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The following quotes come from participants in a recent neonatal randomised controlled trial (RCT) who were interviewed as part of a qualitative substudy.[1] This comment is from a mother who gave consent:

> I remember saying to him, ''Oh great, great, like some effing placebo'' is what I said to him; so, no, I totally understood that idea, so I was kind of glad [because the baby received active treatment.]

This is from a clinician:

> … it's easy for someone to put a gun to your head and say it's your decision. And the gun being that their baby is born and is damaged and is needing a lot of resuscitation and here we are saying, look there's a trial happening and this is the only thing available, and there's nothing else available ….

The quotes illustrate the desperate volunteer problem: RCTs sometimes recruit patients (or their proxies) who are desperate to be placed on one particular arm of the study. They consent because the treatment they desire is available only through that study and are disappointed if randomised to the ''wrong'' arm. The problem usually arises when the RCT is investigating a new treatment into a serious or terminal illness for which current treatment options are limited.

Some argue directly that it is unethical to recruit desperate volunteers to RCTs.[2 3] Others imply that it is unethical by arguing that it is right to recruit only participants who are indifferent between treatment arms.[4] The issue has been discussed most in relation to patients with serious and terminal illness including HIV infection, AIDS[3 5] and variant Creutzfeldt–Jakob disease.[6] In the UK, the parents of two young men with this disease challenged in court the decision of doctors not to use a drug that was still in the early (animal) research stage.[6] This raises the possibility that desperate volunteers could similarly challenge a placebo-controlled RCT.

In this article we defend the recruitment of desperate volunteers into RCTs, provided the condition of equipoise is met. As this is a term used in different ways, we first need to set out what we mean by it. We then set out our argument in more detail and examine it in relation to the arguments of those who believe it is unethical to recruit desperate volunteers. (Throughout this discussion we shall use the term ''equipoise''; others prefer ''uncertainty''.[7 8] This distinction makes no difference of substance here.)

EQUIPOISE

For an RCT to be ethical, a condition of equipoise must prevail. Roughly, this means that there should be no grounds to prefer any particular arm of the trial. Early discussion of equipoise focused on whether the condition should pertain to every clinician.[9–11] The problem is that clinicians often have hunches, anecdotes and evidence of small trials that lead them to prefer a treatment arm. Freedman argued that it is ethical to conduct such an RCT, provided that a condition of collective (or what he termed ''clinical'') equipoise exists—that is, where there is sufficient doubt in the clinical community as a whole.[12 13] The notion of equipoise we intend to use in our argument is akin to Freedman's collective equipoise (although our emphasis on the value element within equipoise is not

Abbreviations: DMEC, Data Monitoring and Ethics Committee; RCT, randomised controlled trial

matched in Freedman's own account). Now let us turn to problems in applying this notion in the justification for recruiting desperate volunteers.

Criticism 1: equipoise is subjective and value based

Being in equipoise implies being uncertain which of two or more treatments is better and, therefore, which to choose. Ambiguities exist, however, in the notions of uncertainty, being better and choice.

Uncertainty

RCTs are powered to avoid error to a certain degree. Typically, they are set up to show an effect to a level where $p \leqslant 0.05$. This means that the researchers can say, roughly, that they will be wrong on 5 of 100 occasions if they conclude that there is an effect. Setting the p value at this level, however, seems arbitrary. Why not choose, say, $p = 0.07$ or $p = 0.03$ (where the researchers can say they will be wrong on 7 of 100 or 3 of 100 occasions if they conclude there is an effect)?

Gifford[14] tackles this question by drawing a distinction between policy decisions and decisions on present patients. We may not have sufficient evidence for a treatment to recommend it in policy guidelines; nonetheless, there may be enough evidence, particularly trends from an RCT, to prefer a treatment arm for a particular patient. Gifford suggests that clinicians may have a different threshold for initiating a treatment for a particular patient and for making a policy recommendation. Any desperate volunteer is likely to take a ''particular patient'' view, desiring the treatment even though it is not yet proved sufficiently enough for a policy decision. Furthermore, in reality, the equipoise is not balanced about the treatment on which evidence of effectiveness is sought, as phase-III RCTs receive funding only if some early-phase trial or case study evidence suggests that the experimental arm may be more effective in treating an illness.[15–17]

Being better

A treatment's being ''better'' is not a matter of fact; it is a judgement based on the facts.[18] For example, mastectomy may offer a slightly higher chance of survival at 5 years than does lumpectomy. Mastectomy, however, is more disfiguring. Which is thought ''better'' will depend on the patient's values: some will prefer the greater chance of survival, others the less disfiguring surgery. If values are crucial to equipoise then surely it is the values of the participants that matter most; the values of the participants should be in equipoise if their participation is to be ethical.[4 19]

Choice

Uncertainty about a treatment's efficacy does not necessarily translate to uncertainty about whether a patient would choose it. Even if patients had no idea whether a treatment may turn out to be efficacious, they may still want it. Typically, this would happen when a person is in a dire situation and the treatment offers hope, distant though it may be. These ambiguities render equipoise incapable of providing justification for RCTs. Indeed, on one account, this was Fried's point when he created the term ''equipoise''.[20]

Criticism 2: equipoise disguises the therapeutic misconception

The opponents of equipoise say that when clinicians enter patients into RCTs, they disavow the therapeutic obligation to recommend and deliver the best treatment. This is because such clinicians no longer deliver individualised care. Instead they are committed to a trial regimen. This has several effects:

- Such regimens are focused on particular end points that are of importance to the researchers but may not be of the same importance to the patient. A clinician may, for example, see that some side effects are particularly important to a patient (as a tremor would be to a concert pianist) and can treat accordingly. In an RCT, the patient's values are set to one side.
- Clinicians committed to a trial regimen cannot make subtle changes in dosage.
- Clinicians cannot follow personal beliefs that the balance of evidence favours one treatment over another.
- Participants in RCTs may be subject to (clinically) unnecessary additional procedures.
- Participants in RCTs may receive inert and pointless placebos.

Opponents of equipoise argue that its use reflects and reinforces a false identification of research with treatment (the ''therapeutic misconception'').[10 11 21–25] Being ''in equipoise'' is supposed to reflect a clinician being unsure of the best action for a patient: the options include entry to trials or individualised care. Equipoise, in so far as it means anything, simply reflects a general lack of knowledge of the effects of treatment on a whole class of patients; in practice, clinicians will always have some notion of which course of action they would prefer to take with a particular patient, including the need for subtle changes of dose and so forth.

Thus, because equipoise is subjective and value based, it cannot provide an objective standard that justifies conducting RCTs. Furthermore, equipoise among clinicians about the effectiveness of a treatment cannot justify disavowing the therapeutic obligation. RCTs can still be justified, but their justification will be based on a set of principles different from those of treatment.[10 26 27] Where beneficence and the best interest of the patient are central to treatment, autonomy and informed consent are central to research. It is permissible to disavow the therapeutic obligation, provided the risks are acceptable and, especially, provided the patient gives informed consent.

Criticism 3: equipoise is used to justify coerced entry to trials

Desperate volunteers provide a vivid illustration of the inadequacy of equipoise. To desperate volunteers, the setting aside of the therapeutic obligation is clear; they strongly believe that there is a better alternative than the one being presented to them by their clinician. Similarly, the failure of fully informed consent is clear; their consent is not truly voluntary; they are effectively coerced into entering the trial. Their subsequent anger at this injustice is shown by their campaigns and court cases.[5]

We shall argue that, at least in some cases, it is not unjust to recruit desperate volunteers. We do this by tackling the three criticisms.

Reply to criticism 1 that equipoise is subjective and value based

Our first task is to suggest a conception of equipoise that is robust enough to do some work in justifying RCTs. The criticism that it cannot do this arises from three ambiguities.

The first ambiguity is about uncertainty: the emergence of trends undermines equipoise for decisions on present patients before we reach the level of statistical certainty necessary for policy decisions. Yusuf,[28] however, looked at the data from several studies on cardiac treatments. Early trends were often deceptive. In one study, aspirin appeared little better than the placebo as a treatment after a heart attack when 3000 patients had been recruited. It was only when 16 000 had been recruited that a clear trend favouring aspirin emerged. More strikingly, a study on administering atenolol after a heart attack had a clear trend suggesting it was

harmful, which did not reverse until 300 deaths had occurred and several thousand patients had been recruited. Yusuf's finding is repeated elsewhere.[29 30] This suggests that Gifford is wrong in postulating a yawning gap between the evidence ethically required for decisions on individual patients and that required for policy decisions. If doctors in the trial on atenolol had made ''particular patient'' decisions then (1) the trial may have collapsed and never have uncovered the truth and (2) the particular patients themselves would have been harmed. Turning to the statistical limits set in trials, these are not arbitrary but rather those that, experience suggests, lead to reliable results in well-conducted RCTs; those that allow for early misleading trends.

Hence, there is no reason to expect clinicians to form strong preferences for a treatment for their patients before they form an opinion about its use for patients in general. Indeed, there is something intuitively odd about the idea that they would. From this we are able to develop a notion of collective equipoise that is more than the headcount of the opinions of personal clinicians: one that is best represented by the Data Monitoring and Ethics Committees (DMECs). They have an overview of the trial data and are able to judge these data against the level of statistical proof required by the protocol. When the DMEC is in equipoise, collective equipoise can be said to prevail.

What of the second ambiguity about the meaning of a treatment being better? The DMEC may be in equipoise over certain end points, but these may not be of importance to the patient. This disjunction in values is, however, likely to be rare. In most cases, the end points of value to researchers, such as disease-free survival, will also be of great value to patients. Were this not the case, the desperate volunteer problem would be echoed in many RCTs—for example, it would be commonplace for people to complain about the group into which they are randomised, for which there seems to be no evidence.[30] In those rare cases of potential major disagreement on the value of end points, researchers will need to ensure that participants are in equipoise (as in the examples for mastectomy or lumpectomy and of the concert pianist; also see a case described by Lilford[31]). In the case of desperate volunteers, however, their concerns are with survival and quality of life; these are matters that researchers will hope the experimental agent tested in the relevant RCT will improve.

We believe this gives us enough to posit a robust conception of clinical equipoise. It is represented by experts conceiving and funding bodies that peer review trials before they start and the DMEC and Trial Steering Committee during a trial. It is based on uncertainty about the effectiveness of one or more trial treatments around end points, which is likely to be widely shared by clinicians and patients. Where it exists, there is a prima facie case for an RCT.

Clearly, this ''expert view'' account of collective equipoise does not equate to having no idea about the efficacy of treatments being tested in an RCT. RCTs begin with a hope that a new treatment will be effective. This hope is based on evidence from other sources (such as phase I and phase II trials) and from positing a plausible mechanism. Such evidence, however, is limited both statistically and in terms of evidence of treatment effectiveness in the clinical situation. RCTs aim at looking at a wider range of end points including compliance, unexpected side effects and the chance that early indications of effectiveness were rogue results. It is this whole picture that will determine whether or not a new treatment is deemed an improvement. And the judgement of this will be a function of values. For example, a treatment may extend life but at the cost of an awful side effect, such as uncontrollable nausea. Thus, when setting up an RCT, clinicians may have strong grounds to believe that a treatment is more effective in terms of a particular end point; what they do not know is its value overall.

Hence, the role of values in collective equipoise means that equipoise does not equate to epistemological uncertainty. This is seen in another way: sometimes clinicians can be epistemologically unsure of the effectiveness of a treatment, but not be in equipoise about its use. An example of this is the argument that an RCT is unacceptable in relation to the use of quinacrine in variant Creutzfeldt–Jakob disease, because the prognosis on the best alternative treatment is so grave.[32] In situations such as these, the clinicians are in agreement with the desperate volunteers; they are not in equipoise. Hence, it does not follow that wherever there is an experimental treatment whose effectiveness is unknown there is collective equipoise. Ex hypothesi, lack of knowledge only justifies an RCT where it exists alongside collective, expert equipoise.

Perhaps, however, this only reinforces the problem of the third ambiguity. Epistemological uncertainty is not necessarily matched by uncertainty of desire and choice. Whereas the values of clinicians may leave them in equipoise, the values of desperate volunteers do not; they will clutch at straws. Does expert collective equipoise justify limiting their options such that the straw they are forced to clutch at is entry into RCTs? Proponents of the idea that research is an activity fundamentally different from treatment would say it is not. The only possible justification for entry into RCTs is informed consent: something absent where consent is coerced. Hence, we must look at the notions of therapeutic obligation and misconception.

Reply to criticism 2 that equipoise disguises therapeutic misconception

Our response to this criticism is that there is no necessary clash between delivering the best available treatment for a patient and resolving uncertainty about the treatment. An aim of well-designed trials is resolving uncertainty for RCTs by delivering the best treatment.[33] In making this claim, it is crucial to separate it from a different dispute on the use of placebos. Much discussion on therapeutic misconception originates in the US where, although the regulatory Food and Drug Administration stipulates that new drugs may be tested against a known effective alternative,[34] placebo trials are preferred in such situations.[35] Like many, we believe this to be unethical and to contravene the Helsinki accord.[36–38] Entering patients into a trial by using placebos in this way would certainly violate the therapeutic obligation. When correctly used, however, placebos represent the best alternative treatment.[17] Provided this is so, clinicians unsure of which treatment is best are acting both in the best interest of the patient and in the interest of ending uncertainty when they enter patients into RCTs.

What, however, of the claim that clinicians entering patients into RCTs cannot give individualised care—for example, by subtly changing treatment regimens? Our response is to ask what is the basis of this care. Presumably, the RCT regimen the clinician wishes to change subtly is based on the best evidence available at the time; what else does the clinician know? The claim that clinical judgement is impaired by RCT regimens seems to parallel the claim that such judgement is impaired by evidence-based medicine in general.[39] Hence, the response to both claims can be the same: ''Psychological research on problem solving and decision making has contributed to these developments—that is, evidence-based medicine and decision analysis—by showing that expert clinical judgment was not as expert as we had believed it to be'' (Elstein,[40] p S135). Plenty of evidence showing the flaws in non-evidence-based clinical judgement is available:[41 42] participants in RCTs are unlikely

to be harmed by being deprived of it. Occasions when particular patients have features that make them exceptional, as in the concert pianist example, are rare. Most of us, however, hover around the average and can often be treated on shared features: try telling an actuary that we are all individuals.[43] The bizarre outcome of the ''individualised care'' argument is that, to paraphrase Smithell's famous dictum, ''it appears unethical to give an unproven treatment to half my patients, but ethical to give it to all of them''.[44]

To summarise, we have suggested that expert, collective equipoise can be robust enough to provide a prima facie case for an RCT. We have denied that RCTs necessarily require a disavowal of the therapeutic obligation. Nonetheless, a central element of the case against the participation of desperate volunteers in RCTs remains: they are effectively coerced into taking part. Similarly, given that equipoise is a function of values, should the values of participants not prevail through the mechanism of (voluntary) consent?[4]

Reply to criticism 3 that equipoise is used to justify coerced entry into trials

Our argument constitutes a rebuttal of the ''difference position'': we have argued that therapeutic research is not fundamentally different from other treatment. As such, it is governed by the same principles, including attention to the best interests of patients. It follows that a way of viewing the difference in equipoise between clinicians and desperate volunteers in RCTs is one to do with what constitutes best interest. Why would clinicians be in equipoise in situations where desperate volunteers clearly are not?

The quinacrine example is a case where the patient's prospects are grave and the potential for harm from the experimental treatment is almost non-existent. Such cases are not typical even in terminal or life-threatening cases. New treatments or procedures that aim at delaying death, reducing the occurrence of disability and so forth can have unexpected and unwanted effects—a treatment may delay death but create unbearable nausea, for example. A choice between, say, immediate death and a possible miracle cure, almost never exists. Thus, one reason for the difference between clinicians and desperate volunteers is that the volunteers' hope for a cure obscures the reality. As one parent we spoke to put it,

> We fully understood what he wanted to do in terms of treatment … we fully understood the side effects if there was going to be any, or the risks involved, but obviously whatever anyone tells you all you listen to is that your child is damaged …[1]

Typically, from the standpoint of collective equipoise, it will be important to discover whether treatments are effective, to allocate resources effectively, to avoid long-term side effects and so on. From the standpoint of the desperate volunteers, these considerations will be of little importance: they will clutch at straws to avoid the harm they face now. RCTs limit their options; the straw they are forced to clutch at is entry into trials. Is this constrained consent justifiable?

Consent to research is generally believed to have two main functions. The first is the protection of the patient against either exposure to a harmful treatment or denial of a therapeutic one. Historically, this is the most important function. The *Nuremberg code* and the *Declaration of Helsinki* developed from the exposure of horrific clinical trials that would never have taken place had voluntary consent been respected.[45 46] The second function is the protection of and respect for the participant's autonomy. This function has taken on increasing importance as our culture has moved away from endorsing medical paternalism.

Our argument thus far on desperate volunteers now enables us to set aside the first function of consent; we do not defend RCTs that harm patients through exposure to or denial of experimental treatments. Thus, the main objection to the recruitment of desperate volunteers is related to autonomy: researchers are manipulating options in such a way as to ensure that desperate volunteers consent to take part in RCTs. Such manipulation generally aims at undermining the voluntariness of consent.[47] It may even constitute coercion. This alone is enough to make it wrong.

We, however, do not live in a libertarian society in which autonomy is considered to be an overarching good. Throughout Western countries, people are denied access to the therapeutic treatments they desire in a number of ways, such as when the treatments are available on prescription only, are illegal or unaffordable. If we believe this to be sometimes or always acceptable then, by extension, we must believe in the principle that a desire for a treatment does not translate into a right to have it. Desperate volunteers are patients who strongly believe in the efficacy of a treatment but who lack the evidence for that belief. Their strength of belief and desire does not translate into a right to receive that treatment. The terms ''coercion'' and ''manipulation of options'' do not apply here, because patients are not wronged when denied access to unproven treatments.

A critic may respond that such patients are wronged because they are harmed psychologically; desperate volunteers are often upset to be presented with limited options and ex fortiori disappointed when allocated to the control group. The wrong occurs if the RCT is unnecessary; the relevant information can be uncovered through other means, such as alternative trial designs with patient preference models of consent,[48 49] historical controlled and epidemiological studies. Alternatively, RCTs may be conducted provided patients had the option of receiving the experimental treatment outside of the trial.

Alternatives to RCTs should always be considered to avoid recruiting desperate volunteers. The option of providing experimental treatments outside of the trial would, however, be acceptable only where most potential participants are not desperate volunteers. Desperate volunteers will always opt for the experimental treatment. In some situations almost all potential participants will be desperate volunteers—as was the case in the trial from which we have taken quotes for this paper. A similar argument would undermine patient preference designs: desperate volunteers will always prefer the experimental arm of the trial. Historical controls deliver poor-quality data: a treatment effect would have to be very large, with no obvious compounding factors, for us to tentatively conclude that it is effective. Hence, if we were to have a treatment that had a useful but not spectacular effect in a desperate situation, we would have no way of discovering this fact. The weaknesses of epidemiology are also well documented—for example, RCTs showing the falsity of epidemiological studies suggesting the protective effect of hormone replacement therapy.[50]

Here is a consequentialist counterargument:[5] desperate volunteers will find ways around the restrictions imposed by RCTs by, for example, sharing their drugs to ensure they get at least some of the active treatment. RCTs will then be scientifically less valid than other approaches. This is perhaps more a practical than a moral consideration and cannot occur in most hospital-based trials. It should, however, focus the minds of the researchers on the moral issue. Our belief is that, in the desperate volunteer situation, if the question can be answered by an alternative to the RCT then it should be. If an RCT is impractical because of resistance from desperate volunteers, in effect the question cannot be answered to the extent that would undermine collective clinical equipoise.

Hence, two types of argument in favour of recruiting desperate volunteers to RCTs exist despite the fact that they would desire an alternative were it made available. The first is, loosely, deontological: that people do not have a right to unproved treatment. (By ''unproved'' we mean that expert, clinical equipoise exists regarding that treatment and the existing best alternative[s].) The second is more consequentialist: disallowing RCTs where there are desperate volunteers would make it difficult to generate and test new treatments in disciplines such as neonatology and end-of-life care where desperation is commonplace.

CLOSING REMARKS

Collective expert equipoise is an essential requirement for setting up an RCT. In other words, there must be doubt in the clinical community on whether a new treatment is better overall than standard treatment. Personal equipoise on behalf of clinicians and participants is desirable and will be present in many cases. Personal equipoise, however, should be seen only as a prima facie criterion.

As a prima facie criterion, personal equipoise is defeasible. Expert, collective equipoise trumps personal equipoise and, where it exists, there is a case for an RCT. Nonetheless, the prima facie criterion sets an important limit. If possible, trials should avoid recruiting desperate volunteers.[31] Situations will, however, exist in which scientific investigation will require randomisation and the recruitment of desperate volunteers. In those situations in which desperate volunteers are recruited, we should seek to minimise the negative effects—for example, by using unequal randomisation in favour of the experimental arm in the trial design.[51 52]

CONCLUSION

It can be ethical to conduct RCTs that recruit desperate volunteers provided there is collective, expert equipoise throughout the course of the trial (as assessed by the DMEC and Trial Steering Committee).

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